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Dietary Phenolics as Reactive Carbonyl Scavengers: Potential Impact on Human Health and Mechanism of Action

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ABSTRACT

Previous studies have demonstrated that accumulation of reactive carbonyl compounds in human tissue will accelerate the vascular damage in both diabetes and uremia. Moreover, advanced glycation progressively and irreversibly modify the proteins over time and yield advanced glycation end products (AGEs). AGEs are thought to contribute to the development of diabetes mellitus and its complications. Therefore, we propose a novel approach to decrease the levels of dicarbonyl compounds by direct trapping of dietary polyphenolic compounds, and consequently, inhibit the formation of AGEs and prevent the development of diabetic complications and age-related diseases.

Key words: Advanced glycation end products, Diabetes, Dietary phenolic compounds, Epigallocatechin-3-gallate, Reactive carbonyl species

REACTIVE CARBONYL SPECIES, ADVANCED GLYCATION END PRODUCTS, AND AGE-RELATED DISEASES

Non-enzymatic modifications of proteins have been implicated in the pathogenesis of diabetes, atherosclerosis, neurodegenerative diseases, and normal aging.[1,2] The modifications can arise from direct exposure to reactive oxygen, chlorine, or nitrogen species, and from reaction with low-molecular-weight reactive carbonyl species (RCS), which originate from a multitude of mechanistically related pathways, like glycation, sugar autoxidation, lipid peroxidation, and UV-photodamage. The accumulation of various RCS such as glyoxal (GO), methylglyoxal (MGO) derived from carbohydrates or lipids, as well as their subsequently induced protein modifications are proposed to constitute a state of "carbonyl stress."[3] These RCS are responsible for the formation of advanced glycation end products (AGEs) and advanced lipoxidation end products (ALEs), and their roles in the development of various aging-related diseases have been increasingly recognized.[4] Higher levels of RCS were observed in the plasma of diabetes patients than in the plasma of healthy people.[5] Therefore, decreasing the levels of dicarbonyl compounds, and consequently, inhibiting the formation of AGEs would be a useful approach to prevent the development of diabetic complications. There is thus a

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prompt need to develop effective strategies to protect from RCS-associated pathogenic conditions, and this will remain one of the major research directions that merit global intention. A very limited number of chemical agents have been found to suppress or prevent excessive generation and accumulation of cellular RCS, and their therapeutic potential has been recognized only recently. These compounds exert their action by interfering with different phases of the reaction cascades, such as by acting as antioxidants, by chelating metal ions, or by directly trapping RCS. As free radical-mediated and oxidative reactions are known to be involved in the process of glycation and lipoxidation, it is not a surprise that antioxidants may be effective inhibitors of glycation and/or lipoxidation in *in vitro* assays. However, numerous clinical trials have failed to provide conclusive evidence for the efficacy of antioxidant therapy in several chronic diseases. These findings have created doubt about the effectiveness of chemical agents that behave solely as antioxidants in alleviating carbonyl stress. An integration of these previous findings and information regarding the formation pathways of RCS, AGEs, and ALEs has enabled us to put forward the hypothesis that chemical agents possessing dual mechanisms of action, namely antioxidant and RCS-trapping activities, are likely to be more promising candidates for developing into disease-preventive agents/pharmaceutical leads for age-related diseases.

TRAPPING OF RCS BY DIETARY PHYTOCHEMICALS

In our studies as well as those of other laboratories, various natural extracts and phytochemicals have been evaluated for their effects on RCS-induced modification of protein structure. Yet, only a very limited number of natural products have demonstrated RCS-trapping capacity.[6-15] In a previous study, we found that epigallocatechin-3-gallate (EGCG) could rapidly trap both MGO and GO under neutral or alkaline conditions. Our data showed that EGCG was more reactive than lysine and arginine in terms of trapping MGO or GO, indicating that EGCG has the potential to compete with lysine and arginine *in vivo* and, therefore, prevent the formation of AGEs. In addition, we also found that EGCG was more reactive at trapping MGO than the pharmaceutical agent, aminoguanidine, which has been shown to inhibit the formation of AGEs by trapping of reactive dicarbonyl compounds *in vivo*.[16]

We have purified three major products from the reaction between EGCG and MGO at a 3:1 mole ratio. Their structures were identified as two mono-MGO adducts and one di-MGO adduct of EGCG with the MGO conjugated at positions 6 and 8 of the EGCG A-ring [Figure 1]. Our results clearly indicate that the major active site of EGCG is at positions 6 and 8 of the A-ring and that the gallate ring does not play an important role in the trapping of reactive dicar-

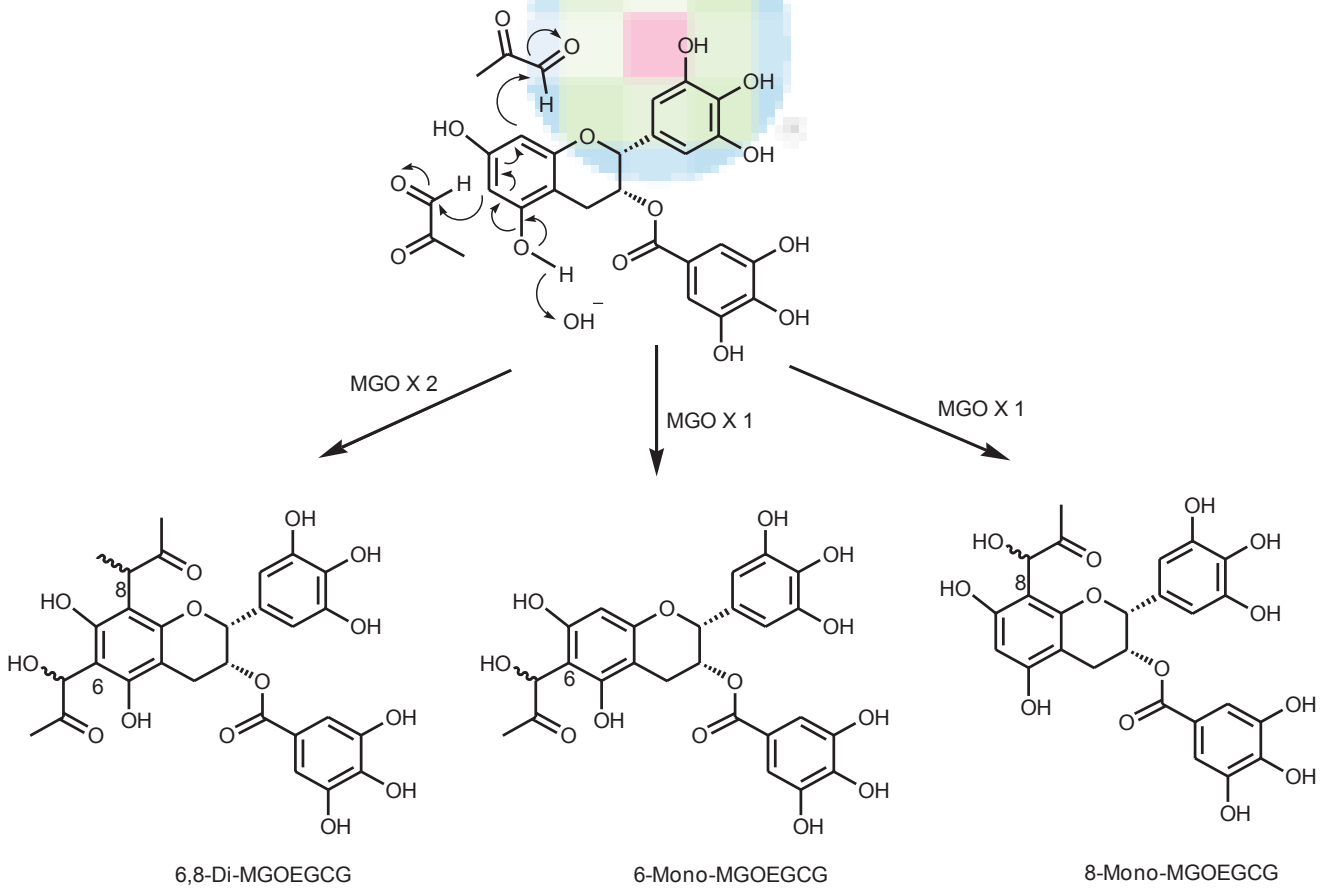

Figure 1. Adducts of methylglyoxal and epigallocathin-3-gallate

bonyl species. The slightly alkaline pH can increase the nucleophilicity at positions 6 and 8 of the A-ring of EGCG, facilitating the addition of MGO at these two positions to form mono- and di-MGO adducts.

Besides EGCG, catechin, epicatechin, theaflavin,[6] proanthocyanidins,[9] phloretin, phloridzin,[10] genistein,[12] curcumin,[14] and a stilbene glucoside from *Polygonum multiforum* Thunb.[11] can effectively trap MGO. Therefore, these compounds represent a new group of 1,2-dicarbonyl scavenging agents. However, these hypotheses must be proven by *in vitro* and *in vivo* studies with the AGEs being accurately analyzed. In addition, different from traditional views on drugs (most drugs elicit their effects via transient interactions with membrane-spanning receptors that modulate cellular signaling pathways), ideally, the carbonyl scavengers should show minimal activity toward drug receptors, thus minimizing unwanted pharmacological effects. Rather, the administration of carbonyl scavengers should proceed in the expectation that they rapidly sequester carbonyl species in cells, thus blocking the adduction of macromolecules and any downstream damages. Whether these phenolic compounds can selectively perform this function also demands further study.

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